APPLICANTS: Bacus *et al.*
U.S.S.N.: 10/735, 118

Amendments to Claims

Kindly cancel claims 1-83 and add new claims 84-110, as indicated in the following complete listing of claims:

Listing of Claims

1-83 (cancelled)

84. (new) A method for identifying a HER-2 over-expressing mammalian tumor that is likely to respond to a HER-2 directed therapy, the method comprising the step of assaying a sample obtained from the mammalian tumor to detect a pattern of expression and/or phosphorylation of:

(a) NDF (Heregulin) polypeptide;

(b) IGFR (Insulin-like Growth Factor Receptor) polypeptide; and optionally

(c) phosphorylated S6 ribosomal polypeptide

wherein the detected pattern of expression and/or phosphorylation identifies whether said mammalian tumor is likely to respond to a HER-2 directed therapy.

85. (new) The method of claim 84, wherein the detected pattern is decreased expression of NDF polypeptide, accompanied by increased expression of IGFR polypeptide in the mammalian tumor as compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as not likely to respond to a HER-2 directed therapy.

86. (new) The method of claim 84, wherein the detected pattern is increased expression of NDF polypeptide, accompanied by increased phosphorylation of S6 ribosomal polypeptide and decreased expression of IGFR polypeptide in the mammalian tumor as

compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as likely to respond to a HER-2 directed therapy.

87. (new) The method of claim 84, wherein the detected pattern of phosphorylated S6 ribosomal polypeptide is determined using an antibody specific for an epitope comprising a phosphorylated serine residue at position 235 in SEQ ID NO: 2.

88. (new) The method of claim 1, wherein said mammalian tumor is a breast tumor.

89. (new) A method for identifying a HER-2 over-expressing mammalian tumor that is likely to respond to a HER-2 directed therapy, the method comprising the step of assaying a sample obtained from the mammalian tumor to detect a pattern of expression and/or phosphorylation of two or more polypeptides selected from the group consisting of:

(a) IGFR polypeptide;

(b) phosphorylated S6 ribosomal polypeptide;

(c) NDF polypeptide;

(d) EGFR (Epidermal Growth Factor Receptor) polypeptide;

(e) phosphorylated AKT polypeptide; and

(f) phosphorylated ERK polypeptide;

wherein the detected pattern of expression and/or phosphorylation identifies whether said mammalian tumor is likely to respond to a HER-2 directed therapy.

90. (new) The method of claim 89, wherein the detected pattern is increased expression of NDF polypeptide, accompanied by increased phosphorylation of S6 ribosomal polypeptide and decreased expression of IGFR polypeptide in the mammalian tumor as compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as likely to respond to a HER-2 directed therapy.

91. (new) The method of claim 89, wherein the detected pattern is decreased expression of NDF polypeptide, accompanied by increased expression of IGFR polypeptide in the mammalian tumor as compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as not likely to respond to a HER-2 directed therapy.

92. (new) The method of claim 89, wherein the detected pattern is decreased expression of NDF polypeptide, accompanied by a decrease in phosphorylation of the S6 ribosomal polypeptide and decreased expression of IGFR polypeptide and in the mammalian tumor as compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as not likely to respond to a HER-2 directed therapy.

93. (new) The method of claim 89, wherein the detected pattern is decreased expression of NDF polypeptide, accompanied by decreased expression of EGFR polypeptide in the mammalian tumor as compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as not likely to respond to a HER-2 directed therapy.

94. (new) The method of claim 89, wherein the detected pattern is decreased expression of NDF polypeptide, accompanied by increased phosphorylation of ERK polypeptide and increased expression of EGFR polypeptide in the mammalian tumor as compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as not likely to respond to a HER-2 directed therapy.

95. (new) The method of claim 89, wherein the detected pattern is increased expression of NDF polypeptide, accompanied by increased phosphorylation of ERK polypeptide and decreased expression of EGFR polypeptide in the mammalian tumor as compared to a

non-tumor tissue or cell sample, wherein said pattern identifies said tumor as not likely to respond to a HER-2 directed therapy.

96. (new) The method of claim 89, wherein the detected pattern is decreased expression of EGFR polypeptide, accompanied by increased phosphorylation of ERK polypeptide in the mammalian tumor as compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as not likely to respond to a HER-2 directed therapy.

97. (new) The method of claim 89, wherein the detected pattern is decreased expression of EGFR polypeptide, accompanied by decreased phosphorylation of AKT polypeptide in the mammalian tumor as compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as not likely to respond to a HER-2 directed therapy.

98. (new) The method of claim 89, wherein the detected pattern is increased expression of IGFR polypeptide, accompanied by increased phosphorylation of S6 ribosomal polypeptide in the mammalian tumor as compared to a non-tumor tissue or cell sample, wherein said pattern identifies said tumor as not likely to respond to a HER-2 directed therapy.

99. (new) The method of claim 89, wherein the detected pattern of expression and phosphorylation or both expression and phosphorylation is determined subsequent to contacting the sample obtained from the mammalian tumor with a HER-2 directed therapy.

100. (new) The method of claim 89, wherein the HER2-directed therapy comprises rhuMAb HER-2.

101. (new) The method of claim 89, wherein the detected pattern of expression, phosphorylation, or both, of one or a plurality of polypeptides (a) through (f) is determined using an antibody, a nucleic acid probe, and/or a peptide probe.

102. (new) The method of claim 89, wherein the detected pattern of phosphorylated AKT polypeptide is determined using an antibody specific for an epitope comprising a phosphorylated serine residue at position 473 in SEQ ID NO: 1.

103. (new) The method of claim 89, wherein the detected pattern of phosphorylated S6 ribosomal polypeptide is determined using an antibody specific for an epitope comprising a phosphorylated serine residue at position 235 in SEQ ID NO: 2.

104. (new) The method of claim 89, wherein the detected pattern of phosphorylated ERK polypeptide is determined using an antibody specific for an epitope comprising a phosphorylated threonine residue at 202 or a phosphorylated serine residue at position 204 in SEQ ID NO: 3.

105. (new) The method of claim 89, wherein the sample obtained from the mammalian tumor is a paraffin-embedded biopsy sample.

106. (new) The method of claim 89, wherein the mammalian tumor is identified as overexpressing HER-2 using an antibody that binds HER-2 polypeptide.

107. (new) The method of claim 89, wherein said mammalian tumor is a breast tumor.

108. (new) A kit for identifying a mammalian tumor that is likely to respond to a HER2-directed therapy, the kit comprising: